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Antibacterial Activity, Toxicity and Drug-Likeness Profiles of *Woodfordia fruticosa*-Derived Metabolites Using Computational-Aided Drug Design Platform

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Abstract: This study presents a comprehensive investigation into the phytoconstituents reported from *Woodfordia fruticosa* (L.) Kurz leaf and flower extracts using gas chromatography-mass spectrometry (GC-MS) analysis, along with some existing phytochemicals, to explore their potential antibacterial properties through molecular docking studies. Followed by bio-assay-guided leave and flower extraction with two solvent systems, i.e., methanol (polar) and petroleum ether (non-polar), was used and further subjected to GC-MS to identify and quantify various secondary metabolites. Based on spectral intensity and volume area, a total of 28 compounds (P1 to P28) have been selected from GC-MS analyses, and an additional 14 compounds (P29 to P42) from previous reports were selected for molecular docking studies against DNA gyrase subunit B (GryB) of *Escherichia coli* (PDB ID: 7P2M) and *Staphylococcus aureus* (PDB ID: 5D7R) with novobiocin as the standard. Further, docking score or binding affinity (kcal/mol.) of each ligand were investigated, where the 4,5-dihydro-4,4-undeca methylene-2-phenyl-1,3-oxazin-6-one (P20) with a docking score of -8.4 kcal/mol., from the GC-MS-derived group and the chrysophanol-8-*O*-β-d-glucopyranoside (P37) with a docking score of -9.7 kcal/mol., from existing phytochemical groups were reported as potential antibacterial. The predicted toxicity and drug-ability profiles also suggested that GC-MS-derived candidates displayed comparatively higher non-toxic profiles but lower drug-likeness profiles than existing groups. This integrative approach explores the phytochemical profiles of *W. fruticosa* responsible for antibacterial activity of the crude extracts and providing insights into in selection of lead antibacterial agent through cost-effective computer-aided drug design platform to accelerate antibacterial drug discovery with higher chance of experimental success.

Introduction

Antibiotic resistance in the 21st century has emerged as a critical global health challenge, posing a threat to the effectiveness of commonly used antibiotics and their ability to combat bacterial infections (GBD 2019; Ranjbar and Alam, 2022; WHO, 2023a). The misuse and overuse of antibiotics in humans, animals and agriculture have accelerated the development of resistant strains, creating a scenario where once-treatable infections become more difficult or even impossible to manage. The consequences of antibiotic resistance include increased morbidity, mortality, prolonged illness and higher healthcare costs (Aslam et al., 2018; GBD 2019; Ranjbar and Alam, 2022; WHO, 2023a). Therefore, the emergence of antibiotic-resistant strains in these diseases underscores the urgent need for global efforts in surveillance, prudent antibiotic use and the development of novel therapeutic strategies to combat this growing public health crisis (Aslam et al., 2018; GBD 2019; Ranjbar and Alam, 2022; WHO, 2023a). Infections

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caused by Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus* can vary widely in terms of severity and associated mortality (Gandra et al., 2019; Frickmann et al., 2023). The outcome of an infection depends on factors such as the specific strain of the bacteria, the site of infection, the overall health of the individual, and the promptness and effectiveness of medical intervention.

To control such infections, both ethnomedicine and modern medicine have their merits. Ethnomedicines have potential without higher side effects, but antibiotics are such active ingredients for quick control that they are expensive and associated with higher side effects (Swain and Padhy, 2015; Yuan et al., 2016; Mazzei et al., 2020; Vaou et al., 2021; Dubale et al., 2023). There is growing recognition of the value of integrating traditional and modern approaches to healthcare (Sarkar et al., 2021; Acharya et al., 2022). This approach, often referred to as 'integrative medicine' or 'complementary and alternative medicine' seeks to combine the strengths of both systems to provide comprehensive and patient-centred care (WHO-2023b; Amare et al., 2023; Sahoo et al., 2022; Park et al., 2019). However, it's crucial to approach such integration with respect for cultural diversity, scientific rigor, and patient safety. Medical practitioners often work together with patients to make informed decisions that consider both traditional and evidence-based medical approaches. To date, researchers have explored the antibacterial activity of many traditional remedies and India's rich diversity of plant species has revealed some with promising antibacterial activities (Aqil and Ahmad, 2007; Swain and Padhy, 2015; Vaou et al., 2019; Chassagne et al., 2021; Balkrishna et al., 2022; Jyotirmayee and Mahalik, 2022). Currently, researchers aim to scientifically validate the antibacterial properties of certain ethnomedicinal practices passed down through generations. Research continues to investigate the mechanisms and efficacy of traditional remedies, with the goal of integrating valuable ethnomedicinal knowledge into modern healthcare practices, especially for treating bacterial infections.

Woodfordia fruticosa (L.) Kurz, commonly known as Dhataki in Sanskrit, is a plant that holds ethnomedicinal significance in traditional Indian medicine systems, particularly Ayurveda, for treatment of diarrhoea, dysentery, bleeding disorders, uterine tonics, astringents, hemostatics, etc. (Das et al., 2007; Dubey et al., 2014; Najda et al., 2021; Rahman et al., 2023). Because it has many types of phytochemicals, such as flavonoids, tannins, phenolic compounds, triterpenoids, and others; as a results able to fight bacteria, reduce inflammation, protect the liver, boost the immune system and keep the heart healthy (Das et al., 2007; Dubey et al., 2014; Najda et al., 2021; Rahman et al., 2023). As a potent antibacterial regimen, it's important to conduct more extensive scientific studies and locate potential phytochemicals needed to fully understand the antibacterial effects and mode of action for their mainstream application. The present study focused on exploring the activity of *W. fruticosa* leave and flower extracts, followed by bio-assay-guided extraction, gas chromatography/mass spectrometry (GC-MS), and computational investigation in a systematic approach.

Materials and Methods

Bio-assay guided extraction of plant parts and GC-MS analysis

From crude extraction of *W. fruticosa* leaves and flowers, we obtained synthetic-grade reagents, solvents, plastic ware, and glassware from SRL and Tarsons Pvt. Ltd., Mumbai, India, through local vendors. The computational work was carried out on a Linux-Ubuntu 16.04 LTS workstation with several cheminformatics software packages (Swain et al., 2022a; Sahoo et al., 2022b). Plant sample *W. fruticosa* leaves and flowers were collected from various small forest patches at the hills of the eastern range of the mountains of India, in the district of Bargarh, Odisha, and identified them with the help of flora of Orissa and other literatures. *W. fruticosa* is locally called as Dhatuk by the tribals of Bargarh district. After washing both plant parts (leaves and flowers) separately with fresh water, we rinsed them in distilled water and shade-dried them at room temperature for 15–20 days. The dried plant parts were crushed using a laboratory blender, and around 200g of dry powder samples were individually extracted using 300 mL of methanol (polar) and petroleum ether (non-polar) in the Soxhlet apparatus for 2 days, followed by the bioassay-guided extraction method. After completion of extraction, it was filtered, dried in a water bath, and stored in an airtight container for further studies. The Turbo Mass Spectrophotometer (USA) model Claurus 590 Gas Chromatography/Claurus SQ 8S Mass Spectrometer (with a liquid auto sampler) carried out the GC-MS study for a retention time of 35 minutes. Then the identified mass spectra were analysed using the NIST library (Konappa et al., 2020; Ralte et al., 2022). The same procedure was used for both solvents (methanol and petroleum ether) and both plant parts (leaves and flowers).

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Ligand and target structure preparation for docking study

Based on high-intensity spectra, we have selected seven constituents WF_ML1-7 or P1 to P7 (from methanol leave extracts), WF_MF1-7 or P8 to P14 (from methanol flower extracts), WF_PL1-7 or P15 to P21 (from petroleum ether leave extracts), and WF_PF1-7 or P22 to P28 (from petroleum ether flower extracts) from GC-MS analyses for computational investigation (Figure S1-S4). As we kwon, GC-MS investigation give the preliminary quantitative information on low molecular weight phytoconstituents; thus based on previous literature, another 14 phytoconstituents, WL_L1-7 or P29 to P36 (leaves from a literature search), and WL_F1-7 or P37 to P42 (leaves from a literature search) for present study. After selection (Table 1), all phytoconstituents know as ligands were retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) along with recorded individual Simplified Molecular Input Line Entry System (SMILE) notation for use in computational study. Further, all ligands structure based optimized and saved in pdb file format for molecular docking study.

We chose DNA gyrase subunit B (GryB) from *E. coli* and *S. aureus* as targets for molecular docking studies based on ethnomedicinal records and a literature review. Therefore, the X-ray crystallographic protein structures of both bacterial GryB were retrieved from the protein data bank with PDB IDs 7P2M (GyrB of *E. coli)* and 5D7R (GyrB of *S. aureus*). Novobiocin (P43*) served as a control antibiotic for both bacterial GyrB during the molecular docking. The molecular docking study was performed using the PyRx 0.8 and AutoDock 4.2 software (Swain et al., 2022a; Sahoo et al., 2022b; Swain and Hussain, 2022). Briefly, the top ten docking poses (kcal/mol.) were generated by each ligand against each bacterial target, and the best pose (the pose with the lowest binding energy produced) was selected accordingly. Further, the protein-ligand 3D and two-dimensional (2D) molecular interactions with targets were visualized using the software BIOVIA-DSV-2019 (Swain et al., 2022a; Sahoo et al., 2022b).

Toxicity profile and lethal dose prediction

After biological activity, the toxicity profile is another crucial parameter to proceed with further investigation or eliminate from the study. Higher toxicity often led to the withdrawal of active candidates from clinical trials, despite their higher therapeutic value. Previously, toxicity profiles were studied using various *in vitro* and *in vivo* models. However, with the advancement of computational tools, it is now possible to predict potential toxicity profiles based on chemical structure by comparing them with a training set dataset (Sahoo et al., 2021; Swain and Hussain, 2022). Therefore, using the ProTox tool (http://tox.charite.de/protox_II/), the possible toxicity profiles—hepatotoxicity (HT), carcinogenicity (CG), immunotoxicity (IT), mutagenicity (MG), cytotoxicity (CT), and lethal dose (LD_{50} in mg/kg) for all 42 phytochemicals (WF_ML1-7, WF_MF1-7, WF_PF1-7, WL_L1-7 and WL_F1-7) and the control antibiotic (http://tox.charite.de/protox_II/).

Physicochemical or Lipinski rule of five profile

The physicochemical profiles, also known as the Lipinski rule (RO5), are another proposed ideal set of parameters to select active oral candidates based on molecular weight, XlogP, number of hydrogen bond acceptors, donors, and tPSA profiles. So, to verify if our selected 42 phytochemicals (WF_ML1-7, WF_MF1-7, WF_PF1-7, WL_L1-7, and WL_F1-7 or P1 to P42) and the control antibiotic would make a good active oral drug candidate, we predicted their physicochemical profiles using the SwissADME tool with reference to the PubChem database (Sahoo et al., 2022b; Swain and Hussain, 2022).

Overall drug-likeness profile prediction

Drug-ability is defined by the ideal characteristics of parameters (physiochemical, toxicity, pharmacokinetic, etc.) that determine whether a chemical has the potential to be marketed as a drug. This is a potential parameter that is only possible through a computational platform to select drug-able candidates from a bunch of chemicals for further study as well as higher clinical success. We used the MolSoft tool (https://www.molsoft.com/) to predict the overall drug-likeness score. Overall, the results help to get some prior information to select some desired candidates to accelerate the drug-development process (Swain et al., 2022a; Swain and Hussain, 2022).

Results and Discussion

Bio-assay guided extraction of plant parts and GC-MS analysis

The quantitative phytochemical study using GC-MS on methanol and petroleum ether extracts of *W. fruticosa* leaves and flowers revealed numerous phytoconstituents with varying molecular weights (Figure S1-S4). From a large set of constituents, we have selected seven constituents from each plant part (Table 1). For better identification, we have divided into different sets, i.e., WF_ML_1 to 7 or P1 to P7 (from methanol leave extracts), WF_MF1-7 or P8 to P14 (from methanol flower extracts), WF_PL_1 to 7 or P15 to P21 (from petroleum ether leave extracts), and WF_PF_1 to 7 or P22 to P28 (from petroleum ether flower extracts) from

GC-MS analyses. Along with this, we have added some existing phytochemicals from a literature survey: we selected another 14 phytochemicals, WL_L_1 to 7 or P29 to P35 (from leaves according to a literature search), and WL_F_1 to 7 or P36 to P42 (from flowers according to a literature search). Overall, the GC-MS study indicated that more candidates were identified from methanol extracts belonging to the alkaloid, phenol/flavonoid, and steroid classes (Table 1). In addition, leaves contain more bioactive phenolic acids, while flower extract contains more flavonoid derivatives.

Table 1. Selected *Woodfordia fruticosa* phytochemicals, WF_ML1-7 (methanol leave extracts), WF_MF1-7 (methanol flower extracts), WF_PL1-7 (petroleum ether leave extracts), and WF_PF1-7 (petroleum ether flower extracts) from GC-MS analyses, along with some phytochemicals from a literature survey, WL_L1-7 (from leaves according to literature search), and WL_F1-7 (flowers according to literature search) for further analyses.

Methanol extracts		Petroleum ether extracts		From literature	
From leaves	From flower	From leaves	From flower	From leaves	From flower
Ethanone, 1-(2,2-dimethyl cyclopentyl)-	3-[4-Acetoxy butyl]-2-oxazolidinone	Cyclohexanol, 3,5-dimethyl-	Undecanal	Betulinic acid	β-sitosterol
(+)-Isomenthol	6,10,13-Trimethyltetradecanol	1-Methoxy-3-(2-hydroxy ethyl)nonane	13-Methyl tetradecanal	Ellagic acid	Chrysophanol-8-*O*-β-D-gluco pyranoside
2-Butenoic acid, 3-(methyl amino-,ethyl ester	4,7,7-Trimethyl-3,9-dioxatricyclo[6.1.0.0(2,4)]nonan-5-one	Trans-1,2,5,5-tetramethyl-3,7,9-trioxa bicyclo(4,2,1) nonane	3-Cyclopentyl propionic acid, 2-methyl propyl ester	Gallic acid	Cyaniding 3,5-diglucoside
Oxirane, hexadecyl-	Hexacosanal	Cyclohexane, 1,1'-(1,4-butanediyl)bis-	Cyclodecanol	Lawsone	Hecogenin
1-[(1-oxo-2-propenyl)oxy]-2,5-pyrrolidine dione	3-Octenoic acid, tridecyl ester	2,10-Dodecadien-1-ol, 3,7, 11-tri methyl-, (z)-	7-octene-2,6-diol, 2,6-dimethyl-	Ursolic acid	Kaempferol 3-*O*-glucoside
N-(2,7-dimethyl-1,7-octadien-3-yl)-2,7-dimethyl -2,7-octadien-1-amine	Cyclopentane, 1-(2-decyl dodecyl)-2,4-dimethyl-	4,5-Dihydro-4,4-Undeca methylene-2-phenyl-1,3-oxazin-6-one	Citronellol	Quercetin 3-O-(6"-galloyl)-β-D-galacto pyranoside	Naringenin 7-glucoside
4-Piperidin-amine, n,1-dimethyl-	2-Octadecyl-propane-1,3-diol	2-Cyclohexe none, 5,5-dimethyl-3-(4-piperidyl) methylamino-	2h-pyran, 2-ethenyltetrahydro-2,6,6-trimethyl-	Oleanolic acid	Quercetin 3-*O*-(6″-galloyl)-β-D-galacto pyranoside

Ligand and target structure preparation for docking study

After retrieval and optimization of both ligands, the control antibiotic was docked against two DNA gyrase subunits B (GryB) of *E. coli* and *S. aureus* (Table 2). Narratively, GC-MS-based 28 candidates showed a docking score of -4 to -8 kcal/mol., against EC-GryB, -4 to -9 against SA-GryB, and the standard novobiocin displayed -7.7 and -8.8 kcal/mol., respectively (Table 2). Briefly, out of 28 GC-MS-based identified phytoconstituents, some compounds have > 5 kcal/mol., against both target enzymes, and those were: P5 (1-[(1-oxo-2-propenyl)oxy] -2,5-pyrrolidinedione) with docking score -5.7 and -5.5, P10 (4,7,7-Trimethyl-3,9-dioxatricyclo [6.1.0.0(2,4)] nonan-5-one) with docking score of -5.0 and -5.4 kcal/mol., P18 (cyclohexane, 1,1'-(1,4-butanediyl)bis-) with docking score -5.9 and -6.3 kcal/mol., P20 (4,5-dihydro-4,4-undeca methylene-2-phenyl-1,3-oxazin-6-one) with docking scores, -7.4 and -8.4, P21 (2-cyclohexenone, 5,5-dimethyl-3-(4-

Table 2. Recorded potency in the form of molecular docking score (kcal/mol.) against two putative bacterial targets with predicted five various toxicity profiles, and LD_{50} (kg/mg.) profiles of selected *Woodfordia fruticosa* phytochemicals (P1 to P42) with the use of the standard antibiotic.

Sl. No.	Selected chemical constituents of *W. fruticosa*	Docking score		Toxicity profiles					
		EC-GryB (7P2M)	SA-GryB (5D7R)	HT	CG	IT	MG	CT	LD_{50}
P1	Ethanone, 1-(2,2-…..	-4.3	-4.9	IA(0.73)	IA(0.65)	IA(0.99)	IA(0.91)	IA(0.78)	25
P2	(+)-Isomenthol	-4.9	-5.4	IA(0.77)	IA(0.89)	IA(0.99)	IA(0.73)	IA(0.88)	940
P3	2-Butenoic acid,3-…	-4.3	-4.5	IA(0.78)	IA(0.51)	IA(0.99)	IA(0.60)	IA(0.72)	2198
P4	Oxirane, hexadecyl-	-4.8	-5.0	IA(0.84)	IA(0.78)	IA(0.79)	IA(0.99)	IA(0.79)	5000
P5	1-[(1-oxo-2-propenyl)…	-5.7	-5.5	IA(0.64)	IA(0.55)	IA(0.99)	IA(0.61)	IA(0.68)	2008
P6	N-(2,7-Dimethyl-1,7-…	-4.3	-5.7	IA(0.82)	IA(0.69)	IA(0.98)	IA(0.84)	IA(0.71)	700
P7	4-Piperidin-amine, *N*,1-..	-4.1	-4.3	IA(0.59)	IA(0.51)	IA(0.98)	IA(0.80)	IA(0.73)	277
P8	3-[4-Acetoxy butyl]-2-…	-4.5	-5.6	IA(0.87)	IA(0.62)	IA(0.93)	IA(0.68)	IA(0.66)	1000
P9	6,10,13-Trimethyltetra…	-4.5	-5.4	IA(0.84)	IA(0.67)	IA(0.99)	IA(0.96)	IA(0.84)	1000
P10	4,7,7-Trimethyl-3,9-dio…	-5.0	-5.2	IA(0.70)	IA(0.52)	IA(0.85)	IA(0.55)	IA(0.76)	1000
P11	Hexacosanal	-4.7	-5.4	IA(0.71)	IA(0.59)	IA(0.95)	IA(0.96)	IA(0.73)	5000
P12	3-Octenoic acid, tri…	-4.3	-5.5	IA(0.76)	IA(0.53)	IA(0.73)	IA(0.98)	IA(0.76)	3000
P13	Cyclopentane,1-(2-….	-4.5	-6.0	IA(0.78)	IA(0.59)	IA(0.88)	IA(0.90)	IA(0.79)	4100
P14	2-Octadecyl-propane-1,3-..	-4.8	-5.7	IA(0.82)	IA(0.56)	IA(0.97)	IA(0.92)	IA(0.89)	2000
P15	Cyclohexanol, 3,5-…	-4.5	-4.9	IA(0.77)	IA(0.76)	IA(0.98)	IA(0.85)	IA(0.85)	940
P16	1-Methoxy-3-(2-hydroxy..	-4.5	-5.1	IA(0.88)	IA(0.61)	IA(0.96)	IA(0.96)	IA(0.87)	5000
P17	Trans-1,2,5,5-tetramethyl-..	-4.6	-5.1	IA(0.84)	IA(0.52)	IA(0.97)	IA(0.58)	IA(0.78)	648
P18	Cyclohexane, 1,1'-(1,4-…	-5.9	-6.3	IA(0.81)	IA(0.51)	IA(0.99)	IA(0.92)	IA(0.87)	15380
P19	2,10-Dode cadien-1-ol,…	-4.9	-5.5	IA(0.79)	IA(0.76)	IA(0.99)	IA(0.97)	IA(0.85)	5000
P20	4,5-Dihydro-4,4-Undeca..	-7.4	-8.4	IA(0.69)	IA(0.53)	IA(0.99)	IA(0.75)	IA(0.72)	172
P21	2-Cyclohexenone, 5,5-…	-5.6	-6.0	IA(0.82)	IA(0.62)	IA(0.97)	IA(0.74)	IA(0.71)	1273
P22	Undecanal	-4.3	-4.7	IA(0.71)	IA(0.59)	IA(0.95)	IA(0.96)	IA(0.73)	5000
P23	13-Methyltetradecanal	-4.4	-5.1	IA(0.71)	IA(0.76)	IA(0.99)	IA(0.91)	IA(0.77)	5000
P24	3-Cyclopentylpropionic…	-5.2	-6.1	IA(0.72)	IA(0.51)	IA(0.99)	IA(0.90)	IA(0.77)	5000
P25	Cyclodecanol	-5.0	-5.4	IA(0.78)	IA(0.75)	IA(0.99)	IA(0.89)	IA(0.84)	1000
P26	7-Octene-2,6-diol, 2,6-…	-4.9	-5.3	IA(0.77)	IA(0.66)	IA(0.99)	IA(0.87)	IA(0.84)	5000
P27	Citronellol	-4.5	-5.8	IA(0.84)	IA(0.65)	IA(0.99)	IA(0.96)	IA(0.86)	3450
P28	2H-Pyran, 2-ethenyl…..	-4.6	-4.8	IA(0.79)	IA(0.63)	IA(0.99)	IA(0.85)	IA(0.80)	4300
P29	Betulinic acid	-6.7	-9.2	IA(0.54)	IA(0.53)	IA(0.74)	IA(0.71)	IA(0.97)	2610
P30	Ellagic acid	-7.5	-8.3	IA(0.83)	IA(0.59)	IA(0.81)	IA(0.84)	IA(0.90)	2991
P31	Gallic acid	-5.3	-5.9	IA(0.61)	IA(0.56)	IA(0.99)	IA(0.94)	IA(0.91)	2000
P32	Lawsone	-5.8	-6.7	IA(0.61)	IA(0.52)	IA(0.70)	IA(0.87)	IA(0.77)	8000
P33	Ursolic acid	-7.1	-9.0	IA(0.52)	IA(0.57)	IA(0.95)	IA(0.85)	IA(0.99)	2000
P34	Quercetin 3-O-(6"-…..	-7.1	-8.5	IA(0.81)	IA(0.85)	IA(0.73)	IA(0.58)	IA(0.65)	5000
P35	Oleanolic acid	-7.4	-7.8	IA(0.52)	IA(0.57)	IA(0.79)	IA(0.85)	IA(0.99)	2000
P36	β-sitosterol	-7.3	-8.6	IA(0.87)	IA(0.60)	IA(0.99)	IA(0.98)	IA(0.94)	890
P37	Chrysophanol-8-*O*-β-D-…	-7.7	-9.7	IA(0.82)	IA(0.70)	IA(0.98)	IA(0.57)	IA(0.79)	3000
P38	Cyaniding 3,5-diglucoside	-7.4	-8.8	IA(0.84)	IA(0.84)	IA(0.60)	IA(0.70)	IA(0.59)	2000
P39	Hecogenin	-8.0	-8.7	IA(0.50)	IA(0.72)	IA(0.97)	IA(0.87)	IA(0.77)	10000
P40	Kaempferol 3-*O*-glucoside	-6.9	-7.7	IA(0.82)	IA(0.85)	IA(0.64)	IA(0.78)	IA(0.69)	5000
P41	Naringenin 7-glucoside	-7.6	-8.4	IA(0.82)	IA(0.85)	IA(0.63)	IA(0.76)	IA(0.69)	2300
P42	Quercetin 3-*O*-(6″-…….	-7.1	-8.3	IA(0.81)	IA(0.85)	IA(0.73)	IA(0.58)	IA(0.65)	5000
43*	Novobiocin	-7.7	-8.8	IA(0.58)	IA(0.66)	IA(0.99)	IA(0.56)	IA(0.56)	962

* Used as standard antibiotic, novobiocin; EC- GryB; *Escherichia coli*- DNA gyrase subunit B; SA-GryB, *Staphylococcus aureus*- DNA gyrase subunit B; HT, hepatotoxicity; CG, carcinogenicity; IT, immunotoxicity; MG, mutagenicity; CT, cytotoxicity; LD_{50}, fifty percent lethal dose (mg/kg).

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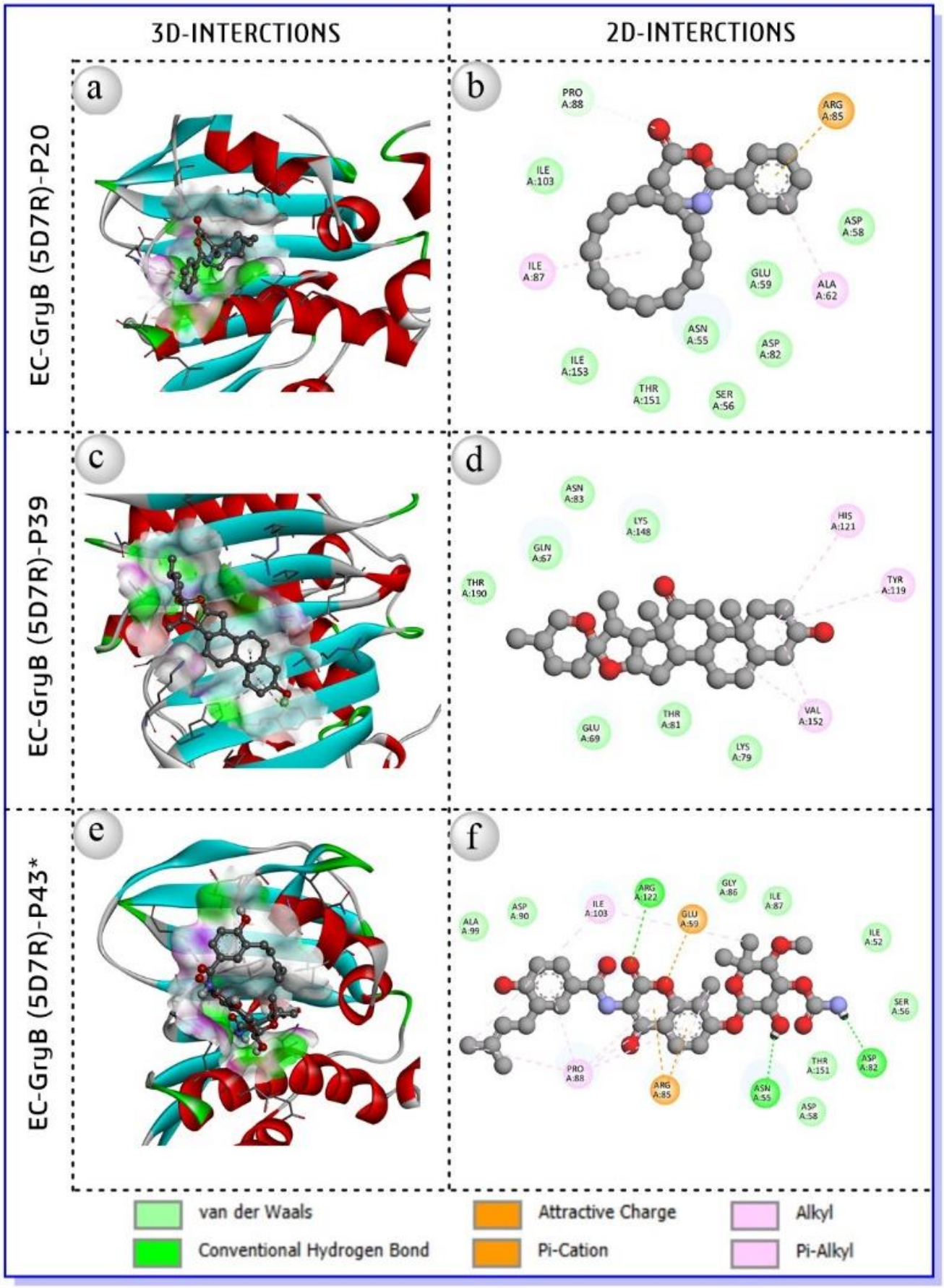

Figure 1. Three-dimensional and two-dimensional protein-ligand interactions of selective potent molecular docking complexes: (a and b), interaction between the most potent GC-MS-derived phytoconstituent, 4,5-dihydro-4,4-Undeca methylene-2-phenyl-1,3-oxazin-6-one (P20) against EC-GryB (5D7R); (c and d), interaction between the most potent literature-based phytoconstituent, hecogenin (P39); and (e and f), interaction between standard antibiotic, novobiocin (P43).

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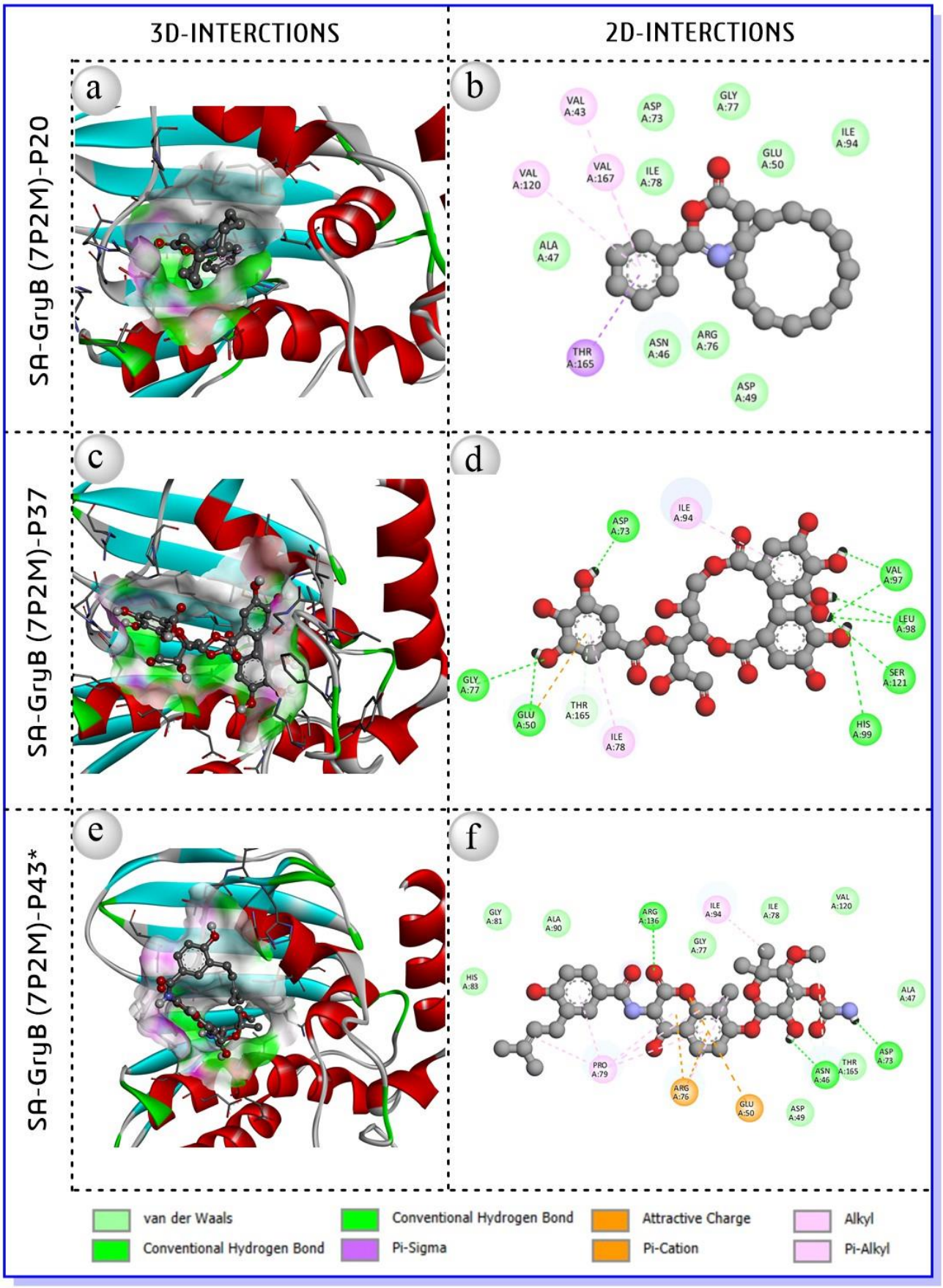

Figure 2. Three-dimensional and two-dimensional protein-ligand interactions of selective potent molecular docking complexes: (a and b), interaction between the most potent GC-MS-derived phytoconstituent, 4,5-dihydro-4,4-Undeca methylene-2-phenyl-1,3-oxazin-6-one (P20) against EC-GryB (5D7R); (c and d), interaction between the most potent literature-based phytoconstituent, chrysophanol-8-O-β-D-glucopyranoside (P37) and (e and f), interaction between standard antibiotic, novobiocin (P43).

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Toxicity profile and lethal dose prediction

The toxicity profiles of all 42 *W. fruticosa*-derived phytoconstituents are recorded in Table 2. Based on profiles with a higher green colour indication, most of the candidates are non-toxic in nature (Table 2). Narratively, GC-MS-derived candidates showed moderate cytotoxicity profiles, while existing candidates showed a higher risk of immunotoxicity with moderate cytotoxicity. The most potential GC-MS-grouped constituent, P20 (4,5-Dihydro-4,4-Undeca methylene-2-phenyl-1,3-oxazin-6-one), showed moderate risk from cytotoxicity, moderate safety from hepatotoxicity, and was highly safe from the rest of the three toxicity profiles. Overall, P2 [(+)-Isomenthol], P15 (cyclohexanol, 3,5-dimethyl-), P19 (2,10-dode cadien-1-ol, 3,7,11-tri methyl-, (z)-), P23 (13-methyltetradecanal), and P25 (cyclodecanol) were the most toxic candidates among all 42 candidates. Similarly, among the 14 candidates in the literature search, the most potential P37 (chrysophanol-8-*O*-β-d-glucopyranoside) existing highly safe four and a moderately safe from mutagenicity profiles. The standard novobiocin displayed a higher risk of immunotoxicity with moderate safety from the rest of the toxicity profiles. In continuation, based on the recorded LD_{50} (mg/kg) value, it was indicated that P15 (cyclohexane, 1,1'-(1,4-butanediyl) bis-) and P38 (cyaniding 3,5-diglucoside) displayed the highest values, 15380 and 10000 mg/kg, respectively (Table 2). Overall results indicated that *W. fruticosa*-derived candidates are non-toxic and safe candidates, where both toxicities for a better antibacterial lead candidate along with LD_{50} values give more insight into selecting the non-toxic dose for further experimentation.

Physicochemical or Lipinski rule of five profile

Based on recorded physicochemical profiles of 28 GC-MS analyses, derived phytoconstituents displayed ideal molecular weight (≤ 500 g/mol.), H-bond donor (≤ 5 number), H-bond acceptor (≤ 10 number), including tPSA (142 Å) defined in standardized RO5 (Table 3). However, most candidate not obeyed the ideal XlogP (≤ 5) profiles and among all, P4 (oxirane, hexadecyl-), P6 (N-(2,7-dimethyl-1,7-octadien-3-yl)-2,7-dimethyl-2,7-octadien-1-amine), P9 (6,10,13-trimethyltetradecanol), P11 (hexacosanal), P12 (3-octenoic acid, tridecylester), P13 (cyclopentane,1-(2-decyldodecyl)-2,4-dimethyl-), P14 (2-octadecyl-propane-1,3-diol), P18 (cyclohexane, 1,1'-(1,4-butanediyl)bis-), P19 (2,10-dode cadien-1-ol, 3,7,11-tri methyl-,(z)-), P20 (4,5-dihydro-4,4-undeca methylene-2-phenyl-1,3-oxazin-6-one), P23 (13-methyl tetradecanal) displayed the higher XlogP value that could be impact on their solubility and metabolisms issues. Literature-based included phytochemicals also not under ideal RO5 profiles like P34 (quercetin-3-O-(6''-galloyl)-β-D-galactopyranoside), P37 (chrysophanol-8-*O*-β-d-glucopyranoside), P38 (cyaniding 3,5-diglucoside) and standard novobiocin have issues with higher molecular weight, P29 (betulinic acid), P33 (ursolic acid), P35 (oleanolic acid), P36 (β-sitosterol) had issues with higher XlogP value, and among all 14 with standard antibiotics have not obeyed the standardized RO5 due to higher molecular weight (Table 3). Overall, from all RO5 parameters, XlogP plays a crucial role, and a candidate must follow the profiles for a higher chance of success in experiments and clinical studies as oral active drug candidates. Simultaneously, as most of the marketed drugs also do not follow the RO5 condition, hard-core restrictions may eliminate more potential candidates. Thus, this predefined parameter gives more relevant information as well as guides to better oral drug candidate selection for higher experimental success.

Overall drug-likeness profile prediction

After evaluating the individual phytoconstituents for potency based on binding efficacy, toxicity, RO5, and lethal dose, we predicted the overall drug-likeness score (Table 3). According to the predicted score, all GC-MS-identified phytoconstituents (P1 to P28) showed negative drug-likeness, while existing candidates (P29 to P42) showed a positive docking score. Particularly, the potential GC-MS-identified candidates P18 and P20 showed -1.02 and -0.99, respectively (Figure 3). In addition, based on the water solubility index, out of 42 phytoconstituents, 8 were very water-soluble, 15 were water-soluble, 13 were moderately soluble, including standard novobiocin, 7 were poor-soluble, and one was insoluble. From bioavailability profiles, three had 0.17 and the rest 0.55. Therefore, drug-ability profiles are an assembly of all individual profiles, and one profile is not defined enough for translational success. Overall, GC-MS tests confirmed the types of phytoconstituents with low molecular weights that were present in the crude extracts, but we did not find any drug-able constituents in our set. Indeed, analyses of existing phytoconstituents indicated that *W. fruticosa* contains a greater number of active and drug-able phytochemicals.

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Table 3. Physicochemical profiles, or Lipinski rule of five, along with the drug-likeness score of selected *Woodfordia fruticosa* phytochemicals (P1 to P42) along with standard antibiotics using bioinformatics tools.

Sl. No.	Selected chemical constituents of *W. fruticosa*	MW	XlogP	H-BD	H-BA	tPSA	DLS	BA	WS
1.	Ethanone, 1-(2,2-…..	140.22	2.3	0	1	17.1	-1.28	0.55	-2.1(S)
2.	(+)-Isomenthol	156.26	3	1	1	20.2	-1.33	0.55	-2.88(S)
3.	2-Butenoic acid,3-…	143.18	1.6	1	3	38.3	-1.19	0.55	-1.49(VS)
4.	Oxirane, hexadecyl-	268.5	8.4	0	1	12.5	-1.52	0.55	-5.83(MS)
5.	1-[(1-oxo-2-propenyl)…	169.13	-0.2	0	4	63.7	-1.74	0.55	-0.58(VS)
6.	N-(2,7-Dimethyl-1,7-…	289.5	7	1	1	12	-0.22	0.55	-5.25(MS)
7.	4-Piperidin-amine, *N*,1-..	128.22	0.39	1	2	15.27	-1.30	0.55	-0.81(VS)
8.	3-[4-Acetoxy butyl]-2-…	201.22	0.5	0	4	55.8	-0.39	0.55	-1.01(VS)
9.	6,10,13-Trimethyltetra…	256.5	7	1	1	20.2	-0.75	0.55	-5.03(MS)
10.	4,7,7-Trimethyl-3,9-dio…	182.22	0.6	0	3	42.1	-1.86	0.55	-1.37(VS)
11.	Hexacosanal	380.7	12.5	0	1	17.1	-1.19	0.55	-8.47(PS)
12.	3-Octenoic acid, tri…	324.5	8.7	0	2	26.3	-1.06	0.55	-6.16(PS)
13.	Cyclopentane,1-(2-….	406.8	14.5	0	0	0	-0.73	0.55	-10.21(IS)
14.	2-Octadecyl-propane-1,3-..	328.6	8.7	2	2	40.5	-1.39	0.55	-6.09(PS)
15.	Cyclohexanol, 3,5-…	128.21	2.2	1	1	20.2	-1.16	0.55	-2.04(S)
16.	1-Methoxy-3-(2-hydroxy…	202.33	3.6	1	2	29.5	-1.10	0.55	-2.71(S)
17.	Trans-1,2,5,5-tetramethyl-.	186.25	1.4	0	3	27.7	-1.95	0.55	-4.01(MS)
18.	Cyclohexane, 1,1'-(1,4-…	222.41	7.9	0	0	0	-1.02	0.55	-5.85(MS)
19.	2,10-Dode cadien-1-ol,…	224.38	5.3	1	1	20.23	-0.86	0.55	-4.05(MS)
20.	4,5-Dihydro-4,4-Undeca..	327.5	6	0	3	38.7	-0.99	0.55	-5.78(MS)
21.	2-Cyclohexenone, 5,5-…	236.35	1.7	2	3	41.1	-0.47	0.55	-2.21(S)
22.	Undecanal	170.29	4.3	0	1	17.1	-1.19	0.55	-3.04(S)
23.	13-Methyltetradecanal	226.40	6.2	0	1	17.1	-1.02	0.55	-4.37(MS)
24.	3-Cyclopentylpropionic…	198.30	3.9	0	2	26.3	-0.15	0.55	-3.16(S)
25.	Cyclodecanol	156.26	2.7	1	1	20.2	-1.83	0.55	-2.49(S)
26.	7-Octene-2,6-diol, 2,6-…	172.26	1.4	2	2	40.5	-1.10	0.55	-1.47(VS)
27.	Citronellol	156.26	3.2	1	1	20.2	-0.93	0.55	-2.94(S)
28.	2H-Pyran, 2-ethenyl…..	154.25	2.4	0	1	9.2	-1.33	0.55	-2.25(S)
29.	Betulinic acid	456.7	8.2	2	3	57.5	0.25	0.55	-7.71(PS)
30.	Ellagic acid	302.19	1.1	4	8	134	-1.11	0.55	-2.94(S)
31.	Gallic acid	170.12	0.7	4	5	98	-0.22	0.55	-1.64(S)
32.	Lawsone	174.15	0.9	1	3	54.4	-0.84	0.55	-1.80(VS)
33.	Ursolic acid	456.7	7.3	2	3	57.5	0.66	0.55	-7.23(PS)
34.	Quercetin 3-O-(6"-…..	616.5	1	10	16	273	0.93	0.55	-4.19(MS)
35.	Oleanolic acid	456.7	7.5	2	3	57.5	0.37	0.55	-7.32(PS)
36.	β-sitosterol	414.71	9.3	1	1	20.23	0.78	0.55	-7.90(PS)
37.	Chrysophanol-8-*O*-β-D-…	634.5	-0.2	11	18	319	0.05	0.55	-3.53(S)
38.	Cyaniding 3,5-diglucoside	611.5	-2.84	11	15	260	0.35	0.55	-1.66(VS)
39.	Hecogenin	430.6	4.8	1	4	55.8	0.04	0.55	-5.55(MS)
40.	Kaempferol 3-*O*-glucoside	448.4	0.7	7	11	186	0.67	0.17	-3.18(S)
41.	Naringenin 7-glucoside	434.4	0.6	6	10	166	0.83	0.55	-2.97(S)
42.	Quercetin 3-*O*-(6″-…….	616.5	1	10	16	273	0.93	0.17	-4.19(MS)
43*	Novobiocin	612.6	3.3	5	11	196	1.11	0.17	-5.34(MS)

*used as standard antibiotic; MW, molecular weight (g/mol.); H-BD, h-bond donor; H-BA, h-bond acceptor; tPSA, topological polar surface area; WS, water solubility (VS, very soluble; S, soluble; MS, moderate soluble; PS, poor soluble); DLS, drug-likeness score; BA, bioavailability.

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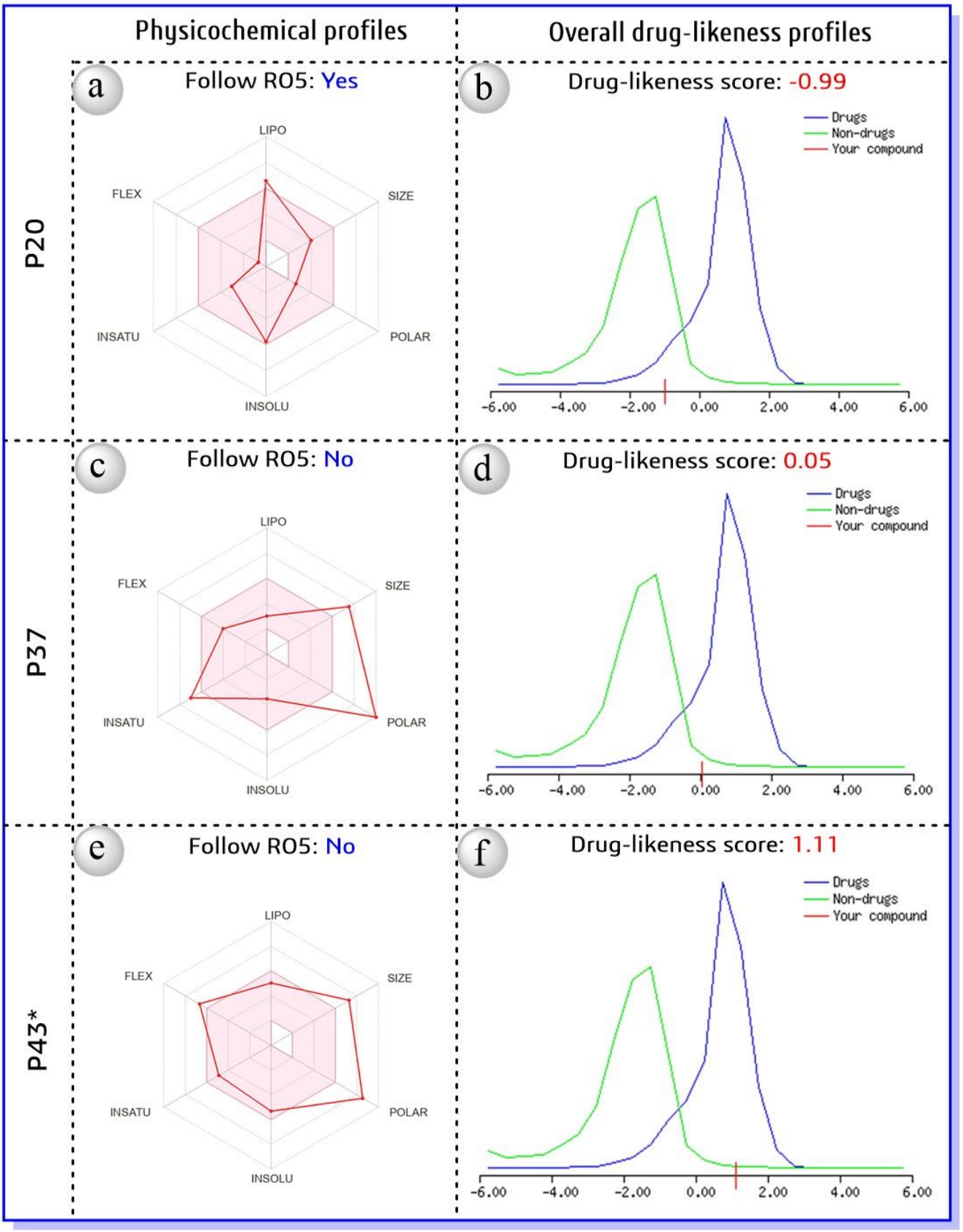

Figure 3. Graphical presentation physicochemical or Lipinski rule of five profiles and overall drug-likeness scores of selected compounds: (a and b), 4,5-dihydro-4,4-Undeca methylene-2-phenyl-1,3-oxazin-6-one (P20); (c and d), chrysophanol-8-O-β-d-glucopyranoside (P37) and (e and f), novobiocin (P43).

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Natural resources, especially medicinal plants, are the most alternative drug source and choice for most research work to use on a complementary, alternative, and repurposing basis (Swain et al., 2022a; Sahoo et al., 2022b and 2022c). Additionally, antibacterial agents derived from various ethnomedicinal crude extracts are non-toxic and possess additive anti-inflammatory and antioxidant potencies, which could aid in improving treatment outcomes and preventing antibiotic resistance. In between, researchers used several advanced techniques and approaches to isolate and locate potential bioactive candidates, where computational tools play a crucial role in accelerating the drug selection process. As a result, both academia and pharmaceutical researchers have implemented various computational tools to preliminary assess the biological potency of natural products derived from different sources before conducting expensive experimental studies.

Generally, crude extracts are composed of various constituents that synergistically show multiple biological activities, but each constituent has a target-specific activity for use in specific therapeutic purposes. Therefore, the identification of such biologically active, drug-able natural phytochemicals is essential to modern drug discovery (Swain et al., 2021a and 2021b). Nevertheless, bioinformatics, or computational validation, is coding and programming-dependent and needs proper hypotheses and expertise to get more reliable results. In addition, a computational-based study cannot recommend the candidate for human consumption, but it is a cost-effective platform to explore the potency, predict the toxicity, and determine the drug-ability profiles, which definitely helps guide a systematic way to select potential leads for more clinical success (Swain et al., 2022a). Overall, this innovative approach not only accelerates the drug discovery process but also provides insights into the molecular mechanisms underlying the antibacterial properties of phytochemicals, paving the way for the development of new and effective natural antimicrobial agents.

Conclusion

The ancient ethnomedical report plays a crucial role in modern drug discovery, where medicinal plants proved themselves by providing more drug candidates to the pharmaceutical market. The present study was focused on identifying potential antibacterial candidates from a well-known non-edible medicinal plant, *W. fruticosa* (leaves and flower extracts). Using a GC-MS study followed by advanced bioinformatics tools, we have identified a large number of constituents with higher docking score and non-toxic profiles, but at last they have not shown ideal drug-likeness profiles (4,5-dihydro-4,4-undeca methylene-2-phenyl-1,3-oxazin-6-one, cyclohexane, 1,1'-(1,4-butanediyl) bis-, etc.). Parallel, we have taken several reported *W. fruticosa*-derived phytochemicals for comparison study, and we have found that all had higher docking scores, non-toxic profiles, and positive drug-ability profiles (chrysophanol-8-*O*-β-d-glucopyranoside, ursolic acid, etc.). In summary, the GC-MS analyses confirmed that *W. fruticosa* crude extracts showed potential antibacterial activity due to the presence of such active constituents, and locating such active candidates through robust bioinformatics is a feasible approach for higher experimental and clinical success.

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Declaration of Competing Interest

The authors declare that they do not have any conflict of interest.

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